Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 3-7, 9, 10-22, 30-35, 38-50, 66, 67, 69-74, 77-81, and 83-86 are pending in the application, with claims 1, 66, and 78 being the independent claims. Claims 2, 8, 23-29, 36, 37, 51-65, 68, 75, 76, 82, 87, and 88-103 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Applicants reserve the right to pursue the subject matter of the canceled claims in related applications. Claims 1, 66, and 78 have been amended to incorporate the recitations of canceled dependent claims. Claim 42 has been amended to make explicit that which was implicit in the claim and the amendment does not narrow the scope of the claim. Claims 3, 4, 7, 9, 10, 30, 33-35, 38, 39, 43, 46, and 50 have been amended to adjust their dependency. These changes are believed to introduce no new matter, and their entry is respectfully requested. Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Information Disclosure Statements

Applicants received return copies of the 1449 forms submitted to the U.S.P.T.O. on July 20, 2000, and on October 23, 2000. However, the latter 1449 form was not initialed by the Examiner. Accordingly, Applicants respectfully request that the documents cited on the PTO form 1449 of the First Supplemental Information Disclosure Statement, filed on

October 23, 2000 be considered, and that an initialed copy of the form be returned to Applicants.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1-10, 15-18, 29-35, 38-50, 66-75 and 77-87 under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification. The Examiner states that, "[t]he specification, while being enabling for administering a plasmid intramuscularly to a mouse having a tumor, wherein said plasmid comprises a nucleic acid sequence encoding IFN-α operably linked to a promoter, wherein said administering causes a decrease in tumor volume, a decrease in tumor metastases and an increase in survival, *does not reasonably provide enablement for any non-infectious, non-integrating DNA, any active fragment of IFN-α, DNA encoding IFN-α that is not operably linked to a promoter, administering the composition to smooth muscle or myocardial tissue, obtaining cell-, tissue- or tumor-specific expression of IFN-α, administering a vector encoding IFN-α as well as another cytokine or treating any symptom of cancer as broadly claimed.*" Applicants respectfully traverse this rejection.

In making a rejection for lack of enablement, the Federal Circuit has stated that the P.T.O. has the burden of initially showing that Applicants' disclosure suggests "an inherently unbelievable undertaking or involve[s] implausible scientific principles." *In re Brana*, 34 USPQ 2d 1436, 1441 (Fed. Cir. 1995).

The documents cited by the Examiner do not meet this burden. In support of his argument, the Examiner cites passages from review articles by Henderson and Blake (*Trends Pharm Sci 13*:145-152 (1992)), Sedlacek (*Crit Rev Oncogenesis 5*:555-587 (1994)),

Dalgleish and Souberbielle (*Cancer Surveys 26*: 289-320 (1995)), Belldegrun *et al.*, (*J. Nat. Cancer Inst. 85*:207-216 (1993)), Santodonato *et al.* (*Human Gene Therapy 7*:1-10, (1996)), Kaido *et al.* (*Int J Cancer 60*:221-229 (1995)), Zhang *et al.* (*Proc Natl Acad Sci USA 93*:4513-4518 (1996)), Zhang *et al.* (*Cancer Gene Therapy 3*:31-38 (1996)), Pestka *et al.*, (WO 97/00085), Miller and Vile (*FASEB J 9*:190-1999 (1995)), Deonarain (*Expert Opin Ther Pat 8*:53-69 (1998)), Verma and Somia (*Nature 389*:239-242 (1997)), Crystal (*Science 270*:404-410 (1995)), and Roth and Cristiano (*J Natl Cancer Inst 89*:21-39 (1997)), that are believed to demonstrate the state of the art with respect to IFN-α and cancer therapy at the time of filing. Applicants respectfully submit that these references are not sufficient to meet the Examiner's burden of showing lack of enablement, as they either: (1) are generalizations based almost entirely on viral vector-based gene therapy techniques, or immunization; (2) contain conclusory statements which have no factual basis demonstrating that Applicants assertions are incredible; or (3) teach methods of IFN-α treatment distinct from those of the instant application.

The Examiner cites several articles which presumably summarize the "state of the art" as to IFN-α therapy. Henderson and Blake is cited only because of the mention of IFN-α in Table 1 which discloses the molecular mass, amino acid content, and major cell source for IFN-α. The majority of the review article teaches the properties of IL-1. This review article was published approximately 5 years prior to the priority date of the instant application, and that a great deal had been learned concerning the properties of IFN-α during that time. The Examiner cites Sedlacek for the proposition that treating tumors is difficult, due to their resistance to immune recognition. As above, this review article was published in 1994, and as such does not reflect the state of the art at the time of filing. The Examiner

cites Dalgleish and Souberbielle, and Pestka *et al.* in support of the importance of IFN-α in generating tumor specific immune responses. The Examiner further cites Belldegrun *et al.*, Santodonato *et al.* Kaido *et al.*, and Zhang *et al.* in support of his assertion that the potential for treating various tumors using *ex vivo* transfected cells expressing IFN-α existed. None of these articles provide data which dispute the enablement of Applicant's invention.

The Examiner then argues that at the time of filing, the combination of vector, promoter, protein and route of administration required to obtain a particular effect and to target desired tissues *in vivo* continues to be unpredictable and inefficient. Applicants respectfully disagree. Here, the Examiner cites Miller and Vile, Deonarain, Verma and Somia, Crystal, and Roth and Cristiano, in support of this assertion.

The Examiner's reliance on Miller and Vile is misplaced. Firstly, this reference is drawn to gene therapy techniques as it relates to gene "replacement" therapy, which is in no way related to the claimed invention. Secondly, the passage cited by the Examiner, is conclusory and provides no factual basis to demonstrate that Applicant's assertions are incredible. Finally, the cited reference was published well before the priority date of the instant application and therefore does not reflect the art at the time of filing.

The Examiner also quotes two generalizations from Deonarain in support of this assertion. The Examiner specifically cites two passages in the review article, one in the introduction and one in the conclusion, that have no factual evidence to support them. The first assertion, that one of the biggest problems hampering successful gene therapy is "the ability to target a gene to a significant population of cells at express it at adequate levels for a long enough period of time[,]" is overly dismissive, and is not supported by data. As shown in this application and other art at the time of filing, IFN-α as well as other cytokines

can be expressed in muscle or other tissue, resulting in systemic expression, and can also be targeted to tumor cells. Secondly, the "technique" which Deonarain compares to viral delivery is the use of ligand-targeted receptor mediated endocytosis. This technique is clearly distinct from the claimed invention and its efficacy bears no relevance to the proposed methods of the instant application.

Although Verma and Somia does discuss to some extent the use of DNA injection, the article is mainly focused on viral vectors. The Examiner quotes passages which generalize as to the state of the art regarding efficiency of delivery and gene expression. As with the Deonarain article, the Examiner has taken the authors' comments out of context, in that the authors primary conclusion appears to be that gene delivery systems "will become as routine as practice as heart transplants are today." (page 242).

In citing the chosen passage from Crystal, the Examiner has taken the message of the article out of context. Citation of this article by the Examiner is incorrect for a number of reasons. First, this article is mainly drawn to viral vectors and not the DNA constructs of the claimed invention. Second, as seen above, the Examiner has chosen to cite a passage which is a conclusory statement and provides no factual evidence that Applicants' assertions are incredible. In doing so, the Examiner has taken the cited passage out of context. As referred to by the author, "However, the logic underlying the potential usefulness of human gene transfer is compelling; and put in a context in which the human genome project will provide 80,000 to 100,000 human genes that could be used in expression cassettes for human gene transfer, *the potential impact of this technology for innovative therapies and increased understanding of human biology is enormous.*" (page 409, last paragraph)(emphasis added).

Roth and Cristiano also teach the use of nonviral vectors and naked DNA, but the Examiner has cited a passage which makes the usefulness of these vectors unclear when taken out of context. As the authors mention, "One of the most promising areas of vector development has been that of nonviral vectors." (page 26, second column). The passage chosen by the Examiner, "that non-viral vectors did not target cells of interest and provided low efficiency[,]" was in response to the problems of obtaining *stable gene transfer* in transfected cells, which is clearly distinct from the methods of the claimed invention.

Taken together, the evidence cited by the above mentioned articles is insufficient to permit one of ordinary skill in the art to conclude that Applicants' invention suggests "an inherently unbelievable undertaking or involve[s] implausible scientific principles." Accordingly, the Examiner has not met the burden required by *Brana*. Based on these remarks, Applicants respectfully request that this rejection be reconsidered and further, that it be withdrawn.

The Examiner has also made several specific objections regarding enablement. Each is discussed below.

(a) The Examiner asserts that the specification does not compare plasmids to other vectors such that one of skill could administer any non-infectious, non-integrating DNA encoding IFN-α to treat cancer. Applicants respectfully traverse this rejection.

Claims 1, 66, and 78, as amended, are drawn to delivery of a non-infectious, non-integrating DNA administered to muscle or a body cavity. Such DNA molecules are clearly enabled by the specification, as exemplified by the delivery of plasmids and non-infectious viral genomes. "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the

claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) and M.P.E.P. 2164.01(b). As the Examiner states, the specification has clear support for delivery of plasmids, in addition, the specification supports the use of non-infectious DNA virus genomes (page 72, lines 12-20). Based on this disclosure, one of ordinary skill in the art would easily be able to make and use any DNA as claimed. Based on these remarks, Applicants respectfully request that this objection be reconsidered, and further that it be withdrawn.

(b) The Examiner also asserts that the specification does not teach any active fragment of IFN-α that would treat cancer. Applicants respectfully disagree.

Under the Federal Circuit standard for enablement, some necessary experimentation by the skilled artisan is permitted; the amount of experimentation, however, must not be unduly extensive. *Atlas Powder Co. v. E. I. duPont de Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984). Furthermore, patent claims that include some claimed combinations which are inoperative are not necessarily invalid under 35 U.S.C. § 112. *Id.* Factors to be considered when determining whether the amount of experimentation is undue were set out in *In re Wands*, 858 F.2d 731 at 737 (Fed. Cir. 1988).

Two factors to be considered in determining whether undue experimentation is required are "the amount of direction or guidance presented," and "the state of the prior art." *See Wands* 8 USPQ2d 1400 at 1404. In the present application, clear guidance on the nature of an active fragment of IFN-α is disclosed by the following: (1) an *active fragment* of IFN-α is defined in the specification as a fragment of the cytokine that displays the antiproliferative activity of the mature or full length cytokine (page 32, lines 22-23), (2) assays for screening antiproliferative activity are disclosed, and additional assays are

routine, and (3) methods of making the fragments are disclosed and are also routine. Therefore, one of ordinary skill in the art could easily make and screen fragments for activity using only routine experimentation. Furthermore, *active fragments of hIFN-α* are disclosed in the specification, *e.g.*, polypeptides comprising amino acids 83-166 of SEQ ID NO:10, amino acids 61-166 of SEQ ID NO:10, amino acids 41-166 of SEQ ID NO:10, and amino acids 21-166 of SEQ ID NO:10 (page 33, lines 1-5).

An additional factor to be considered in determining whether undue experimentation is required is "the quantity of experimentation necessary." *See Id.* With respect to producing and screening selected fragments of IFN-α for activity, the entire process would be considered by the skilled artisan as a single "experiment," much as the entire attempt to make a monoclonal antibody (*i.e.*, from a diverse population of hybridomas) is considered as a single "experiment " in *Wands*. *See* 8 USPQ2d 1400 at 1407. Based on these remarks, Applicants respectfully request that this objection be reconsidered, and further that it be withdrawn.

(c) The Examiner also asserts that the specification does not enable cases where the DNA encoding IFN-α is not operably linked to a promoter. While not acquiescing to the Examiner's objection, and solely to advance prosecution, Applicants have amended claims 1, 66, and 78 to recite that the claimed DNA encoding a cytokine is operably associated with a promoter. Accordingly, the Examiner's objection is rendered moot and should be removed.

(d) The Examiner also asserts that the specification does not enable administering the composition to smooth muscle, myocardial tissue, any body cavity, or the peritoneal cavity. Examples 6 and 7 provide experimental evidence of the success of systemic cytokine expression following intraperitoneal injection. In addition, Losordo *et al.*,

Circulation 98:2800-2804 (1998) (Exhibit A), the authors presented clinical results showing increased myocardial perfusion and improved collateral blood flow in human heart patients following injection of DNA encoding VEGF. The dosages, and dosage frequencies used in this document follow directly from the teachings provided in the captioned application. The authors observed clinical findings which were indicative of increased vascular supply in all of the treated patients, clearly a therapeutic effect. Therefore, delivery of DNA to myocardium (smooth muscle) has been shown, and extending this to delivery of cytokines is routine, and clearly enabled. Based on these remarks, Applicants respectfully request that this objection be reconsidered, and further that it be withdrawn.

(e) The Examiner also asserts that the specification does not enable obtaining cell-, tissue- or tumor-specific expression of IFN-α. Applicants respectfully disagree. It is well known in the art that promoter and enhancer regions regulate cell- and tissue-specific transcription of polynucleotides. Pages 68-72 of the specification clearly teach the construction of polynucleotide constructs used in the claimed invention, including the addition of transcriptional control regions such as promoters and enhancers (page 72, lines 2-5). Also, Example 6 of the specification teaches a method of treating malignant tumors of murine ovarian carcinoma via intraperitoneal injection of cytokine-expressing plasmid DNA. This method results in, among others, "(2) *targets tumor ascites*, rather than peritoneal tissues (suggesting that systemic cytokine effects should be reduced using this method, (3) inhibits tumor growth and enhances survival,..." (page 111, line 24). Therefore, this example teaches a method to target ovarian cancer cells via intraperitoneal injection. Example 7 teaches the selective transfection of malignant cells in the murine intraperitoneal melanoma tumor model. This method also selectively transfects tumor tissue (Tables 4-6),

even when the cytokine-expressing plasmid is injected intraperitoneally. Based on these remarks, Applicants respectfully request that this objection be reconsidered, and further that it be withdrawn.

(f) Lastly, the Examiner asserts that the specification does not enable administering a vector encoding IFN-α as well as another cytokine. Applicants respectfully disagree. The Examiner provides no evidence refuting the enablement of these claims. Pages 53 and 54 of the specification teach a single polynucleotide construct containing more than one polynucleotide sequence encoding one or more molecules. Not only is there enabling support for the co-administration of cytokines in the specification, this technique was also well known to those in the art at the time of filing, as evidenced by Sasaki *et al.* (*Journal of Immunology, 159*:3638-3647 (1997)) (Exhibit B). Sasaki *et al.* teaches that immunization of a DNA vaccine with *IL-12 and granulocyte-macrophage colony-stimulating factor (GM-CSF)*-expressing plasmids induces strong immune responses against HIV-1 antigens.

Due to the abundance of support in both the specification and in the art at the time of filing, and in view of the enablement requirements set forth in *In re Brana, In re Fisher,* and *In re Wands, supra,* Applicants respectfully request reconsideration and withdrawal of the Examiner's enablement rejection.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-10, 15-18, 29-35, 38-50, 66-75 and 77-87 have been rejected by the Examiner under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing

to particularly point out and distinctly claim the subject matter of the invention. Applicants respectfully traverse this rejection.

Claims 8 and 29 are rejected because they do not further limit claims 1 or 2. Claims 8 and 29 have been canceled, therefore the Examiner's rejection has been rendered moot and should be removed.

Claim 42 is allegedly indefinite because the Examiner asserts that the meaning of "operably encodes" is unclear. While not acquiescing to the Examiner's rejection, Applicants have amended claim 42 to recite, that the "DNA encodes at least one additional cytokine, or active fragment thereof, through an operable association with a promoter, wherein said additional cytokine is expressed *in vivo*." An operable association, as defined in the specification (page 71, lines 10-23), is, "[w]hen a polynucleotide encoding a gene product, *e.g.*, a polypeptide, is associated with one or more regulatory sequences in such a way as to place expression of the molecule under the influence or control of the regulatory sequence(s). Two DNA fragments (such as a polypeptide-coding polynucleotide and a promoter associated with the 5' end of the polynucleotide) are "operably associated" if induction of promoter function results in the transcription of mRNA encoding the desired gene product and if the nature of the linkage between the two DNA fragments does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of the expression regulatory sequences to direct the expression of the gene product, or (3) interfere with the ability of the DNA template to be transcribed. Thus, a promoter region would be operably associated with a polynucleotide encoding a polypeptide if the promoter was capable of effecting transcription of that polynucleotide." Based on the amendment to claim

42, and these remarks, Applicants respectfully request that this rejection be reconsidered, and further that it be withdrawn.

Claims 44 and 45 are rejected because the Examiner asserts that the metes and bounds of "cell specific" and "tissue specific" cannot be determined. It is clear to those skilled in the art that the phrase cell specific denotes cells of the same type (*i.e.* macrophages) and that the phrase tissue specific denotes specificity to a particular tissue. Therefore, Applicants believe that the Examiner's assertion is incorrect and respectfully request withdrawal of the rejection.

The Examiner has rejected claims 4, 39, 40, and 46 under 35 U.S.C. § 112, second paragraph, for allegedly containing improper Markush groups. Applicants respectfully traverse these rejections. The Examiner has stated that certain elements in the Markush groups may be embraced by more than one member of the Markush groups recited in the claims. For example, the Examiner suggests that in claims 4, 39 and 46, "[h]ead and neck cancer" can be a number of the cancers listed such as melanoma[,]... that "cationic lipids, cationic peptides or cationic proteins are cationic polymers[,]"... and that "gene therapy or immunotherapy can also be considered a type of chemotherapy."

The M.P.E.P clearly states that "double inclusion of an element by members of a Markush group is not, in itself, sufficient basis for objection to or rejection of claims." For example, it is stated that a Markush group reciting "amino, halogen, nitro, chloro and alkyl" groups is acceptable even though "halogen" is generic to "chloro." M.P.E.P. § 2173.05(h). The stated P.T.O. policy is that "there is no per se rule of indefiniteness concerning overlapping members where alternatives are recited in a claim, *e.g.*, a Markush group[, and that] . . . the facts of each case must be evaluated to determine whether or not the multiple

inclusion of one or more elements in a claim gives rise to indefiniteness in that claim." M.P.E.P. § 2173.05(o).

Applicants maintain that the elements in the Markush groups cited by the Examiner are not indefinite. For example, one of ordinary skill in oncology in reading claim 4 would easily understand the distinction between "head and neck cancer," a commonly used term in the art, and melanoma, just as easily as one of ordinary skill in the chemical arts would understand the distinction between generic "halogen" and "chloro." Head and neck cancer is a classification of cancer, defined in Harrison's, "Principles of Internal Medicine" (McGraw-Hill, New York, 14th Edition) (Exhibit C) as epithelial carcinomas of the head and neck that arise from the mucosal surfaces in the head and neck area (chapter 89, page 549). A solid cutaneous tumor is also distinct. Metastases of cancers are tumors which form in other parts of the body, *but are of the same origin as the original cancer* and therefore cannot encompass, for example, prostate carcinoma as a metastasis of melanoma, as asserted by the Examiner.

Additionally, the cationic peptides of claims 39 and 40 are easily distinguishable from the more generic "cationic proteins." It is well known to those of ordinary skill in the art that peptides are defined as small protein fragments. Claim 39 also defines cationic polymers as comprising cationic compounds, *other than lipids or peptides*.

Finally, it is well known to those of ordinary skill in the art that gene therapy, immunotherapy, and chemotherapy, as recited in claim 46, are distinct forms of therapy *when used in terms of a treatment for cancer or metastases*. Gene therapy denotes that the primary therapeutic is intervention using genetic material, chemotherapy involves chemical

intervention (such as the chemicals listed on specification page 47, line 24-page 48 line 12), and immunotherapy involves the administration of immunomodulatory compounds.

Therefore, since the Examiner has not evaluated the facts giving rise to alleged indefiniteness, Applicants respectfully request that the rejections based on improper Markush groups be withdrawn.

Claim 42 is rejected as allegedly being unclear as to the claimed construct. Claim 42 clearly reads on additional copies of polynucleotides encoding the same cytokine (*e.g.* IFN-α) and polynucleotides encoding additional heterologous cytokines. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

Due to amendment and clarification of the claims, Applicants respectfully request reconsideration and withdrawal of all rejections under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 1-10, 15-18, 29-35, 38-50, 66-75, and 77-87 under 35 U.S.C. § 102(b) as allegedly being anticipated by Horton (Feb. 1999, PNAS, Vol. 96, pages 1553-1558). The Examiner states that the parent case 09/196,313 was unavailable at the time of writing the office action and this rejection was made in case the parent case did not enable the instant claims. Although upon filing of the instant application, Applicants were under no obligation to provide a copy of copending applications, Applicants are submitting herewith a courtesy copy of U.S. Application No. 09/196,313, filed on November 20, 1998, which clearly predates Horton, *et al.* Applicants assert that, upon review, the Examiner will find support for all of the pending claims in the priority application. Therefore, the Examiner's rejection is incorrect and should be removed.

The Examiner has rejected claims 66, 67, 69, 71, 75, 78-80, 83, and 87 under 35 U.S.C. § 102(e) as allegedly being anticipated by Pestka *et al.* (WO 97/00085, Jan. 3, 1997). The claims of the instant invention are distinct, because as opposed to Pestka *et al.*, the claimed invention is a method of treating cancer comprising *administering a non-infectious, non-integrating polynucleotide construct into the body cavity of a mammal* in such as way as to result in local and systemic expression of the polypeptide encoded by the polynucleotide. This is clearly distinct from Pestka *et al.* which teaches the *ex vivo* transfection of tumor cells with a polynucleotide, followed by introduction of said transfected tumor cells subcutaneously into a mouse to obtain expression of the polynucleotide *in vivo*. Applicants also wish to note that Pestka *et al.* only teaches *subcutaneous* administration of tumor cells, while the methods of the rejected claims involves administration of non-infectious, non-integrating DNA encoding a cytokine into the *body cavity* of a mammal. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

In the Claims:

Claims 2, 8, 23-29, 36, 37, 51-65, 68, 75, 76, 82, 87, and 88-103 have been canceled.

The following claim 1 was substituted for the pending claim 1:

1. (Once amended) A method of treating cancer or metastasis thereof in a mammal, comprising:

administering into a muscle of said mammal a non-infectious, non-integrating DNA encoding a cytokine or an active fragment thereof, through operable association with one or more transcription control elements, wherein said one or more transcription control elements comprises a promoter; and wherein said DNA is administered free from *ex vivo* cells;

such that the cytokine encoded by said DNA is expressed *in vivo*, and

such that said cytokine is present in the blood stream of said mammal in an amount effective to treat said cancer, or metastasis thereof.

The following claim 3 was substituted for the pending claim 3:

3. (Once amended) The method of claim [2] 1, wherein said one or more transcription control elements comprises a polyadenylation signal and transcription termination signal.

The following claim 4 was substituted for the pending claim 4:

4. (Once amended) The method of claim [2] 1, wherein said cancer is selected from the group consisting of renal cell carcinoma, colorectal carcinoma, lymphoma, Kaposi's sarcoma, melanoma, prostate cancer, ovarian cancer, lung cancer, liver cancer, head and neck cancer, bladder cancer, uterine cancer, bone cancer, leukemia, breast cancer, non-melanoma skin cancer, glioma, solid cutaneous tumor, epidermoid carcinoma, metastases of any of thereof, and combinations of any of thereof.

The following claim 7 was substituted for the pending claim 7:

7. (Once amended) The method of claim [2] 1, wherein said muscle tissue is selected from the group consisting of skeletal muscle, smooth muscle, or myocardium.

The following claim 9 was substituted for the pending claim 9:

9. (Once amended) The method of claim [2] 1, wherein said cytokine is selected from the group consisting of IFNω, IFNα, IFNτ, IFNγ, IFNβ, IL-1, IL-2, IL-4, IL-7, IL-12, IL-15, IL-18, GM-CSF, and a combination of any of thereof.

The following claim 10 was substituted for the pending claim 10:

10. (Once amended) The method of claim [2] 1, wherein said active fragment of a cytokine is selected from the group consisting of an active fragment of IFNω, an active fragment of IFNα, an active fragment of IFNτ, an active fragment of IFNγ, an active fragment of IFNβ, an active fragment of IL-1, an active fragment of IL-2, an active fragment of IL-4, an active fragment of IL-7, an active fragment of IL-12, an active fragment of IL-15, an active fragment of IL-18, an active fragment of GM-CSF, and a combination of any of thereof.

The following claim 30 was substituted for the pending claim 30:

30. (Once amended) The method of claim [29] 1, wherein said cancer is melanoma or metastasis thereof.

The following claim 33 was substituted for the pending claim 33:

33. (Once amended) The method of claim [29] 1, wherein said cancer is glioma.

The following claim 34 was substituted for the pending claim 34:

34. (Once amended) The method of claim [29] 1, wherein said cancer is epidermoid carcinoma.

The following claim 35 was substituted for the pending claim 35:

35. (Once amended) The method of claim [2] 1, wherein said DNA is dissolved in an aqueous solution.

The following claim 38 was substituted for the pending claim 38:

38. (Once amended) The method of claim [2] 1, wherein said DNA is administered free from association with transfection-facilitating proteins, viral particles, liposomes, cationic lipids, and calcium phosphate precipitating agents.

The following claim 39 was substituted for the pending claim 39:

39. (Once amended) The method of claim [2] 1, wherein said DNA is administered as a complex of said DNA and one or more cationic compounds selected from the group consisting of cationic lipids, cationic peptides, cationic proteins, cationic polymers other than lipids or peptides, and mixtures thereof.

The following claim 42 was substituted for the pending claim 42:

42. (Once amended) The method of claim [2] 1, wherein said DNA [operably encodes one or more additional cytokines.] encodes at least one additional cytokine, or active fragment thereof, through operable association with a promoter, wherein said additional cytokine is expressed *in vivo*.

The following claim 43 was substituted for the pending claim 43:

43. (Once amended) The method of claim [2] 1, wherein said DNA comprises a region regulating gene expression.

The following claim 46 was substituted for the pending claim 46:

46. (Once amended) A method of treating cancer, or metastasis thereof, in a mammal, comprising:

the method of claim[2] 1 in combination with one or more additional cancer treatment methods selected from the group consisting of surgery, radiation therapy, chemotherapy, immunotherapy, and gene therapy.

The following claim 50 was substituted for the pending claim 50:

50. (Once amended) The method of claim [2] 1, wherein said mammal is human.

The following claim 66 was substituted for the pending claim 66:

66. (Once amended) A method of treating cancer in a mammal, comprising:

administering into a body cavity of said mammal a non-infectious, non-integrating [polynucleotide construct comprising a polynucleotide] DNA encoding a cytokine, or an active fragment thereof, through operable association with a promoter, and wherein said DNA is administered free from *ex vivo* cells or *ex vivo* cellular material; such that said cytokine is delivered to a tumor in a therapeutically effective amount.

The following claim 78 was substituted for the pending claim 78:

78. (Once amended) A method of selectively transfecting malignant cells in a body cavity of a mammal, comprising:

administering into a body cavity of said mammal a non-infectious, non-integrating [polynucleotide construct comprising a polynucleotide] DNA encoding a molecule, or an active fragment thereof, through operable association with a promoter, and wherein said DNA is administered free from *ex vivo* cells or *ex vivo* cellular material; such that said molecule is delivered substantially to and expressed in malignant cells within said body cavity.